Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 38, No. 1, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01310-9

EDITORIAL COMMENT

Autoimmunity, Immunoglobulin Adsorption and Dilated Cardiomyopathy: Has the Time Come for Randomized Clinical Trials?*

Douglas L. Mann, MD, FACC
Houston, Texas

Over the past 10 to 15 years there has been increasing evidence suggesting that abnormalities in cellular and humoral immunity may contribute to the overall pathogenesis of dilated cardiomyopathy. Circulating autoantibodies to a variety of cardiac antigens including G-protein–linked receptors (such as those to $beta_1$-adrenoreceptors and muscarinic receptors), mitochondrial antigens, adenosine diphosphate, adenosine triphosphate carrier proteins and cardiac myosin heavy chain have been identified in patients with dilated cardiomyopathy (1–4). Immunization with certain cardiac muscle antigens such as alpha-myosin heavy chain can result in the development of a dilated cardiac phenotype in certain susceptible strains of mice (5). Moreover, it has been possible to demonstrate either cardiodepressant (6,7) or cardiostimulatory effects (8) for some circulating autoantibodies. Nonetheless, a precise interpretation of the above findings has been complicated by the knowledge that low titers of autoantibodies, which can be part of the normal immunlogic repertoire, are not always pathogenetic. For example, tissue injury secondary to ischemia or infection may lead to autoantibody production because of alterations of self-antigens or exposure of antigens that are normally sequestered from the immune system. In such situations, the generation of autoantibodies is the result, and not the cause, of the tissue injury. Furthermore, observations about autoimmune responses are generally made in patients with established disease; accordingly, any inferences regarding cause and effect are, invariably, indirect and circumstantial.

See page 178

If cardiac autoantibodies do play a role in either the initiation or progression of dilated cardiomyopathy, then it follows that their removal would be expected to lead to disease stabilization or improvement. Conversely, if cardiac autoantibodies are simply markers of the underlying autoimmune process, then efforts to remove them would not lead to an improvement in clinical outcomes. With these considerations in mind, the report by Schimke et al. (9) in this issue of the *Journal* is of particular interest. Schimke et al. (9) present data suggesting that immunoadsorption results in a significant lowering of a portfolio of plasma markers indicative of oxidative stress, including thiobarbituric acid-reactive substances (TBARS), anti-oxidized low-density lipoprotein autoantibodies and lipid peroxides (LPO) in patients with dilated cardiomyopathy. Moreover, the changes in TBARS levels correlated with changes in New York Heart Association (NYHA) functional class ($r = 0.34$, $p = 0.08$), whereas the changes in LPO levels were inversely correlated with changes in left ventricular ejection fraction ($r = -0.33$; $p = 0.08$). Although this interesting study must be viewed as provisional because of the small numbers of patients, this study raises the broader question of whether it is time to consider performing randomized clinical trials with immunoadsorption in patients with dilated cardiomyopathy. Before addressing this issue, however, it is first appropriate to review what is known clinically about immunoadsorption in dilated cardiomyopathy.

Immunoadsorption and dilated cardiomyopathy. The technique of immunoadsorption, which first gained popularity for treating patients with familial heterozygous hypercholesterolemia (10), has also been used to treat patients with a variety of autoimmune diseases, including myasthenia gravis, systemic lupus erythematosis, Guillain-Barré syndrome and Sjörgren syndrome. Removal of autoantibodies with immunoadsorption is achieved by passing a patient's plasma over columns that contain immobilized antibodies against immunoglobulin (IgG) kappa and lambda light chains and IgG heavy chains. To prevent infectious complications that might arise from inappropriate lowering of circulating IgG levels, intravenous (IV) IgG is often given back at the end of a period of treatment (IgG replacement therapy). Immunoadsorption depletes a variety of circulating immunoglobulins, including autoantibodies, alloantibodies (i.e., antibodies directed against antigens from a genetically distinct member of the same species) and circulating immune complexes.

Immunoadsorption for patients with dilated cardiomyopathy was first reported in an uncontrolled pilot study by Wallukat et al. (11), who showed that this technique efficiently removed circulating antibodies directed against the $beta_1$-adrenoreceptor. They also observed an improvement in NYHA functional class in patients ($n = 8$) with dilated cardiomyopathy. This study was soon followed by another pilot study that reported an improvement in short-term hemodynamic effects in nine patients with severe (NYHA functional class III and class IV) heart failure, who were refractory to conventional medical therapy

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Winters Center for Heart Failure Research, Cardiology Section, Department of Medicine, Baylor College of Medicine, and the Houston Veterans Administration Medical Center, Houston, Texas. This communication was supported by research funds from the N.I.H. (P50 HL-O6H and RO1 HL58081-01, RO1 HL61543-01, HL-42250-10/10).

(angiotensin-converting enzyme [ACE] inhibitors, digitalis, diuretics and IV beta-blockers) (12). In this study, Dorffel et al. showed that immunoadsorption resulted in a significant improvement in cardiac output and a significant decrease in left ventricular filling pressure and systemic vascular resistance (12). However, these early studies lacked a concurrent control group. Recently, the hemodynamic effects of immunoadsorption have been reported (13) in 18 patients with dilated cardiomyopathy who were randomized for three months to immunoadsorption and subsequent IgG replacement or conventional therapy (ACE inhibitors, digitalis, diuretics). Felix et al. (13) showed that immunoadsorption and IV IgG administration resulted in a significant improvement in cardiac index and stroke volume index, as well as a decrease in systemic vascular resistance, whereas no significant change occurred in these parameters in the control group.

Most recently, Müller et al. (14) studied 34 patients with idiopathic dilated cardiomyopathy (NYHA functional class II or worse) who had high circulating titers of autoantibodies directed against the $beta_1$-adrenoreceptors. All patients were receiving standard heart failure therapy, including ACE inhibitors, digitalis, diuretics and oral beta-blockers. In this case-control study, the first 17 patients received standard therapy, whereas the next 17 patients received immunoadsorption (without IgG replacement therapy) for five consecutive days; patients were then followed serially for one year. The investigators reported that immunoadsorption therapy resulted in a significant lowering of anti-$beta_1$-adrenoreceptor antibodies in the treatment group, whereas the anti-$beta_1$-adrenoreceptor antibody titer remained unchanged in the control group. Within one year of treatment, there was a significant (≈70%) increase in ejection fraction and a significant (≈15%) decrease in left ventricular end-diastolic dimension in the treatment group, whereas no significant changes occurred in these parameters in the untreated patients (14). Thus, taken together, the above studies suggest that immunoadsorption leads to improvements not only in left ventricular structure and function but also in functional status in selected patients with dilated cardiomyopathy.

Is there sufficient evidence to support the initiation of randomized clinical trials with immunoadsorption therapy for patients with dilated cardiomyopathy? Before addressing this question, it is perhaps important to identify the existing gaps in our knowledge with respect to immunoadsorption in patients with dilated cardiomyopathy. First, and perhaps foremost, it will be important to identify the subsets of patients with dilated cardiomyopathy that will benefit the most from immunoadsorption therapy. In this regard, the extant literature does not delineate whether all patients with dilated cardiomyopathy will benefit from immunoadsorption therapy, or whether patients with elevated levels of circulating autoantibodies (e.g., anti-$beta_1$-adrenoreceptor antibodies) should be studied. It should also be emphasized that immunoadsorption can be quite expensive (≈$30,600/patient/year [14]). Thus, this technique should not be used indiscriminately. Presumably, patients with high autoantibody titers would benefit the most. However, it is also reasonable to ask whether myocardial biopsies should also be used to look for markers of immune activation in select patients.

Second, the mechanism(s) of action of immunoadsorption is not known. Although studies have demonstrated decreases in circulating autoantibodies, it is not at all clear that a cause-and-effect relationship has been established. Furthermore, immunoadsorption can lead to a decline in systemic vascular resistance independent of the removal of circulating auto-antibodies (15). Thus, part of the hemodynamic benefit that has been observed may be nonspecific. In this issue of the *Journal*, Schimke et al. (9) present data from a substudy from the previous report by Müller et al. (14). These investigators raise the interesting possibility that alterations in oxidative stress levels may have been responsible for the salutary effects observed following immunoadsorption (9). Although the study by Schminke et al. (9) is carefully done, the number of patients in each group ($n = 9$) is too small to draw meaningful conclusions. Moreover, the correlations between the changes in levels of oxidative stress and improvements in clinical outcomes are modest. Thus, these interesting studies should be viewed as provisional and/or hypothesis-generating.

A third gap in terms of our understanding of immunoadsorption therapy for dilated cardiomyopathy is that the optimal strategy for immunoadsorption has yet to be determined. Different investigators use different protocols and different immunoadsorbent devices. Moreover, the use of IgG replacement in some of the immunoadsorption protocols may in and of itself lead to improvements in clinical status for patients with dilated cardiomyopathy, as has recently been shown by Gullestad et al. (16). Thus, it will be imperative to optimize immunoadsorption protocols for patients with dilated cardiomyopathy.

Finally, it is not clear from existing studies whether immuoadsorption alone, which would be expected to modulate humoral immunity, will be sufficient in the long term, or whether it may be necessary to incorporate strategies that lead to suppression of cellular-mediated immunity as well. Nonetheless, despite the gaps in our knowledge base that are detailed above, the existing studies, as well as the recent report by Schimke et al. (9) in this issue of the *Journal*, suggest that immunoadsorption therapy for dilated cardiomyopathy has progressed well beyond phenomenology and has matured to the extent where randomized clinical trials would appear to be warranted for selected groups of patients. In this regard, one might envision three treatment arms: conventional therapy, conventional therapy plus immunoadsorption and conventional therapy plus immunoadsorption plus IV IgG replacement. Ideally these studies would be conducted in a blinded manner (no easy task) and would be performed, at least initially, in selected patients chosen on the basis of high circulating titers of auto-

JACC Vol. 38, No. 1, 2001
July 2001:184–6

antibodies and/or findings consistent with immune activation on myocardial biopsy. Although the cost of such a study will likely be substantial, if properly done, the results of such a study would almost certainly be priceless in terms of the new insights that it would provide into the pathogenesis of dilated cardiomyopathy.

Acknowledgments

The author acknowledges Mary Helen Soliz for her secretarial assistance, and thanks Dr. Andrew I. Schafer for his past and present support and guidance.

Reprint requests and correspondence: Dr. Douglas L. Mann, Cardiology Research (151), V A Medical Center, 2002 Holcombe Boulevard, Houston, Texas 77030. E-mail: dmann@bcm.tmc.edu.

REFERENCES

1. Limas CJ, Goldenberg IF, Limas C. Autoantibodies against β-adrenoceptors in human idiopathic dilated cardiomyopathy. Circ Res 1989;64:97–103.
2. Klein R, Maisch B, Kochsiek K, Berg PA. Demonstration of organ-specific antibodies against heart mitochondria (anti-M7) in sera from patients with some forms of heart diseases. Clin Exp Immunol 1984;58:283–92.
3. Caforio ALP, Grazzini M, Mann JM, et al. Identification of α- and β-cardiac myosin heavy-chain isoforms as major autoantigens in dilated cardiomyopathy. Circulation 1992;85:1734–42.
4. Schultheiss HP, Bolte HD. Immunological analysis of auto-antibodies against the adenine nucleotide translocator in dilated cardiomyopathy. J Mol Cell Cardiol 1985;17:603–17.
5. Liao L, Sindhwani R, Leinwand L, Diamond B, Factor S. Cardiac alpha-myosin heavy chains differ in their induction of myocarditis. Identification of pathogenic epitopes. J Clin Invest 1993;92:2877–82.
6. Schulze K, Becker BF, Schauer R, Schultheiss HP. Antibodies to ADP-ATP carrier—an autoantigen in myocarditis and dilated cardiomyopathy—impair cardiac function. Circulation 1990;81:959–69.
7. Fu ML, Schulze W, Wallukat G, Hjalmarson A, Hoebeke J. A synthetic peptide corresponding to the second extracellular loop of the human M2 acetylcholine receptor induces pharmacological and morphological changes in cardiomyocytes by active immunization after 6 months in rabbits. Clin Immunol Immunopathol 1996;78:203–7.
8. Wallukat G, Wollenberger A, Morwinski R, Pitschner HF. Anti-$beta_1$-adrenoceptor autoantibodies with chronotropic activity from the serum of patients with dilated cardiomyopathy: mapping of epitopes in the first and second extracellular loops. J Mol Cell Cardiol 1995;27:397–406.
9. Schimke I, Müller J, Priem F, et al. Decreased oxidative stress in patients with idiopathic dilated cardiomyopathy one year after immunoglobulin adsorption. J Am Coll Cardiol 2001;38:178–83.
10. Richter WO, Jacob BG, Ritter MM, Suhler K, Vierneisel K, Schwandt P. Three-year treatment of familial heterozygous hypercholesterolemia by extracorporeal low-density lipoprotein immunoadsorption with polyclonal apolipoprotein B antibodies. Metabolism 1993;42:888–94.
11. Wallukat G, Reinke P, Dorffel WV, et al. Removal of autoantibodies in dilated cardiomyopathy by immunoadsorption. Int J Cardiol 1996;54:191–5.
12. Dorffel WV, Wallukat G, Baumann G, Felix SB. Immunoadsorption in dilated cardiomyopathy. Ther Apher 2000;4:235–8.
13. Felix SB, Staudt A, Dorffel WV, et al. Hemodynamic effects of immunoadsorption and subsequent immunoglobulin substitution in dilated cardiomyopathy: three-month results from a randomized study. J Am Coll Cardiol 2000;35:1590–8.
14. Müller J, Wallukat G, Dandel M, et al. Immunoglobulin adsorption in patients with idiopathic dilated cardiomyopathy. Circulation 2000;101:385–91.
15. Schulze K, Becker BF, Schultheiss HP. Antibodies to the ADP/ATP carrier, an autoantigen in myocarditis and dilated cardiomyopathy, penetrate into myocardial cells and disturb energy metabolism in vivo. Circ Res 1989;64:179–92.
16. Gullestad L, Aass H, Fjeld JG, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. Circulation 2001;103:220–5.